CHAPTER

5

The Brain Initiative—Implications for a Revolutionary Change in Clinical Medicine via Neuromodulation Technology

Elizabeth M. Mosier[1], *Michael Wolfson*[2], *Erika Ross*[1], *James Harris*[3], *Doug Weber*[4,5], *Kip A. Ludwig*[1]

[1]Mayo Clinic, Rochester, MN, United States; [2]National Institute of Biomedical Imaging and Bioengineering, Bethesda, MD, United States; [3]ECS Federal, Arlington, VA, United States; [4]Defense Advanced Research Projects Agency, Arlington, VA, United States; [5]University of Pittsburgh, Pittsburgh, PA, United States

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INTRODUCTION – THE BRAIN INITIATIVE

Launched in April 2013, the White House Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is a "bold new research effort to revolutionize our understanding of the human mind and uncover new ways to treat, prevent, and cure brain disorders like Alzheimer's, schizophrenia, autism, epilepsy, and traumatic brain injury (BRAIN Initiative, 2014)" (see Fig. 5.1). The BRAIN Initiative includes participation from numerous companies, research universities, foundations, and philanthropic organizations (Fact Sheet: BRAIN Initiative, 2013). The BRAIN Initiative grew out of the Obama Administration's "GRAND Challenges" program to forward ambitious but achievable goals that require advances in science and technology (21st Century Grand Challenges, 2013). The driving motivation for the BRAIN Initiative is to accelerate the development of new technologies enabling researchers to produce dynamic pictures of the brain showing how individual brain cells and complex neural circuits interact with unprecedented spatial and temporal resolution (Fact Sheet: BRAIN Initiative, 2013). By developing new technology to better understand the brain, the expectation is that the concomitant improvement in fundamental understanding will ultimately revolutionize therapies for brain disorders.

Mental and neurologic disorders and diseases are estimated to already cost the United States $1.5 trillion per year (Nager and Atkinson, 2016), and in 2016, the 21st Century Cures Act was signed into law to establish legislative commitment to funding this essential research. The 21st Century Cures Act provided the National Institutes of Health (NIH) with $4.8 billion for the Precision Medicine Initiative, a program established for genetics of disease research, Former Vice President Biden's "Cancer Moonshot" cancer research program, and the BRAIN Initiative, as part of the NIH Strategic Plan (21st Century Cures, 2016).

The goals of the BRAIN Initiative are particularly germane to the development of next-generation noninvasive and implantable devices to stimulate and record from the human nervous system as a therapy. These devices make up a rapidly growing area of medical device technology, often known as neuroprosthetic, neuromodulation, bioelectronic medicine, or electroceutical devices, but for the purposes of this book, these devices will be called "neuromodulation

FIGURE 5.1 Director of the NIH, Dr. Francis Collins, introducing President Barack Obama for the BRAIN Initiative.

devices." In 2014, LifeScienceAlley estimated there to be more than 1000 active clinical trials in neuromodulation, with more than 1300 different therapeutic indications being pursued preclinically (Matter et al., 2015).

Neuromodulation therapies have already demonstrated remarkable efficacy in subsets of patients who are refractory to existing drug options in applications such as chronic pain, hypertension, epilepsy, and Parkinson disease. However, there is only limited understanding of their underlying physiologic mechanisms of action (MOAs). Through the development of new technology to improve our understanding of neuromodulation therapies – and a fundamental commitment to sharing of data and experimental best-practices across government, industry, academia, and philanthropic institutions – there is remarkable potential for economic benefit and therapeutic growth in this sector.

HISTORY

The initial seed for the BRAIN Initiative began at a special symposium facilitated by the Kavli Foundation in 2011. This symposium included 27 preeminent neuroscientists and nanoscientists. It was titled, "Opportunities at the Interface of Neuroscience and Nanoscience," and it was at this meeting that the idea of creating a brain activity map was introduced. The proposed goal for a brain activity map was to simultaneously record every action potential from every neuron within a circuit and, ultimately, within the whole brain (Alivisatos et al., 2012; The BRAIN Initiative, 2016). Although it was recognized that the technology to accomplish this feat did not yet exist, it was posited that, with recent advances in optogenetic stimulation, optical recordings, and miniaturized implantable transducers, simultaneously recording and precisely manipulating single-neuron function in the brain would be achievable in the not-too-distant future. The impetus provided by this initial meeting led to a series of additional brain activity map symposia and workshops, also facilitated by the Kavli Foundation, and eventually led to a brain activity map white paper that was submitted to the White House Office of Science and Technology Policy. This white paper became the initial template for what would become the White House BRAIN Initiative (Alivisatos et al., 2012, 2013).

The direct inspiration for the Kavli efforts was the previously successful Human Genome Project (HGP), an international collaborative research project with the goal of providing a complete map and understanding of the human genome. According to an independent analysis performed by Battelle Memorial Institute in Columbus, OH, the $3.8 billion investment in the HGP led to $796 billion in economic impact by 2011 (Tripp and Grueber, 2011). In the early stages of the HGP, gene sequencing technology was too costly and slow to sequence the estimated 3 billion base pairs that compose it. Strategic investment in new technologies that did not exist before the onset of the HGP was required to reach the aggressive milestones laid out in the initial proposal. Moreover, the ambitious work to be accomplished required coordinated research efforts and minimally restricted data sharing between federal agencies, foundations, academic institutes, and industry at an international scale (Table 5.1).

Although the brain activity map proposal provided the initial framework that formed the foundation of the BRAIN Initiative (Markoff and Gorman, 2013; Markoff, 2013), each institution participating in the BRAIN Initiative conducted their own planning effort and outlined their own goals, consistent with their own unique missions. Consequently, the overarching goals of the BRAIN efforts have changed from an explicitly stated goal of measuring all of the action potential from all neurons in the human brain simultaneously, to a general commitment to "accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought" (BRAIN, 2025, 2014). A list of current participating institutions follows (Fact Sheet: BRAIN Initiative, 2013); however, this list is expected to expand significantly over the life of the BRAIN Initiative:

INITIAL GOVERNMENT CONTRIBUTORS

Some of the initial government contributors to the BRAIN Initiative were the National Institutes of Health (NIH), the Defense Advanced Research Projects Agency (DARPA), and the National Science Foundation (NSF). Combined, these organizations proposed investments of $110 million for fiscal year 2014. These government organizations were interested in the development of novel devices, technologies, and applications that could improve, enhance, or advance current understanding and treatment of neurologic function.

INITIAL PRIVATE SECTOR PARTNERS

Initial private contributors, including the Allen Institute for Brain Science, the Howard Hughes Medical Institute, and the Kavli Foundation, invested a combined $122 million in the first year of the BRAIN Initiative. These investments came from both existing and new campaigns and were aimed at developing neural activity maps, imaging technology, and an effort to increase collaborations across different areas of neuroscience. These private sector contributors offered groundbreaking models of scientific discovery from which the BRAIN Initiative adopted many of

TABLE 5.1 BRAIN Initiative Partnerships (BRAIN Initiative Partners, 2016)

BRAIN Initiative Partnerships			
Federal Agencies	**Foundations**	**Institutes**	**Industry**
National Institutes of Health (NIH)*	Brain & Behavior Research Foundation	Howard Hughes Medical Institute	Blackrock
National Science Foundation (NSF)	Pediatric Brain Foundation	Salk Institute for Biological Studies	Boston Scientific
Defense Advanced Research Projects Agency (DARPA)	Kavli Foundation		General Electric
U.S. Food and Drug Administration (FDA)	National Photonics Initiative		GlaxoSmithKline
The Intelligence Advanced Research Projects Activity (IARPA)	Simons Foundation		Inscopix
	Allen Institute for Brain Science		Lawrence Livermore National Laboratory
			Medtronic
			NeuroNexus
			NeuroPace
			Ripple
			Second Sight
***National Institutes of Health Partners**			
National Center for Complementary and Integrative Health (NCCIH)			
National Eye Institute (NEI)			
National Institute on Aging (NIA)			
National Institute on Alcohol Abuse and Alcoholism (NIAAA)			
National Institute of Biomedical Imaging and Bioengineering (NIBIB)			
National Institute of Child Health and Human Development (NICHD)			
National Institute on Drug Abuse (NIDA)			
National Institute on Deafness and Other Communication Disorders (NIDCD)			
National Institute of Neurological Disorders and Stroke (NINDS)			
National Institute of Mental Health (NIMH)			

its core principles. For example, the Allen Institute maintains a "commitment to an open science model within its research institutes," while the Kavli Foundation and its noted philanthropist founder, Fred Kavli, have invested in the development of research institutes worldwide (Allen Institute, 2016; Kavli Foundation, 2016). Similarly, the Howard Hughes Medical Institute has focused investments on investigator development and the support of innovative scientific pioneers (HHMI, 2016). Combined, these partners provided a model of support for cutting-edge research and information dissemination.

NIH Planning Efforts

Given that the NIH was funding several billion dollars in neuroscience research each year, NIH planning efforts were focused on soliciting input from diverse experts, both in and out of the NIH-funded neuroscience community. The goal was to better understand how a planned, highly coordinated, and sustained effort, leveraging a comparatively much smaller additional amount of funding, could be used to address gaps overlooked by traditional investigator-initiated funding mechanisms. NIH Director Francis Collins—who had previously served as the head of the Human Genome Project—organized an Advisory Committee to the Director to inform the initial planning of the NIH BRAIN efforts. This consisted of leading neuroscientists, engineers, clinicians, and industry partners. The Advisory Committee to the Director, in conjunction with the Office of the Director, convened several workshops to solicit and synthesize input from the wider community over the course of the first year, covering diverse topics such as molecular approaches to understanding the brain, large-scale recording techniques, structural biology, computational theory, data science, and human neuroscience. These deliberations were distilled into the BRAIN 2025 Report, which outlined the long-term scientific plan to serve as the guide for the NIH BRAIN Initiative (BRAIN, 2025, 2014).

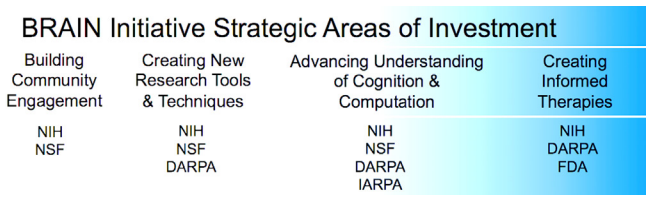

FIGURE 5.2 Government agency division of strategic investments.

The BRAIN 2025 Report called for a sustained federal commitment of $4.5 billion over 12 years. The NIH also identified a group of external advisors, known as the BRAIN Multi-Council Working Group, which convenes several times a year to advise the NIH Program Staff on how to best implement the recommendations in the BRAIN 2025 Report in light of emerging opportunities (Fig. 5.2).

BRAIN INITIATIVE PROGRAMS FOR NEUROMODULATION THERAPIES

The programs under the White House BRAIN Initiative include efforts that are both directly and indirectly intended to affect neuromodulation therapies, either by improving our fundamental understanding of the functional neural circuitry of the brain or by developing new tools that could be used to directly observe and optimize the effects of neuromodulation therapies in real-time. For example, the initial NIH BRAIN 2025 Report highlighted seven "high-priority" areas that have now been implemented as funding programs. These areas are.

1. **Discovering diversity** to identify and provide experimental access to the different brain cell types for determining their roles in health and disease,
2. **Building maps at multiple scales** to generate circuit diagrams that vary in resolution from synapses to the whole brain,
3. **Imaging the brain in action** to produce a dynamic picture of the functioning brain by developing and applying improved methods for large-scale monitoring of neural activity,
4. **Demonstrating causality** to link brain activity to behavior with precise interventional tools that change neural circuit dynamics,
5. **Identifying fundamental principles** to produce conceptual foundations for understanding the biological basis of mental processes through development of new theoretical and data analysis tools,
6. **Advancing human neuroscience** to develop innovative technologies to understand the human brain, treat its disorders, create and support integrated human brain research networks, and
7. **Moving from BRAIN Initiative to the brain** to integrate new technological and conceptual approaches produced in goals 1 through 6 to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease.

This list of priorities provides a useful framework to describe efforts from other institutions, which can generally be categorized under these seven priorities. BRAIN Initiative Programs, which were developed to directly address, at least in part, issues pertaining to neuromodulation therapies, are described next. This effort leverages and involves experts spanning 10 of the 27 institutes and centers at the NIH. Each of these contributors brings mission relevance to and expertise on the disorders and pathologies being addressed by the BRAIN Initiative.

NIH BRAIN PROGRAMS FOR NEUROMODULATION THERAPIES

The goal of the NIH BRAIN Programs for Neuromodulation is to incentivize work on key gaps that could be catalytic but that do not fare well in traditional NIH grant review. Traditional NIH reviewers place significant emphasis on innovation without incorporating any project-related risks, discourage serial dependency of tasks, and require rigorous experimental design with detailed power analyses to justify the number of subjects. This overwhelming focus on innovation, unwillingness to accept risky project elements, and avoidance of serial dependency of tasks may disadvantage studies characterizing fundamental mechanisms of stimulation, combining multiple pre-existing stimulation modalities to enhance effect, or testing engineering refinements in the clinic necessary to move from a single proof-of-concept demonstration to a practical therapy with a clear business case for industry investment. A list of currently-active NIH funding announcements can be found at https://www.braininitiative.nih.gov/funding/index.htm.

NIH PROGRAMS TO SUPPORT NONINVASIVE NEUROMODULATION STRATEGIES

Recently, the NIH has released several new Requests for Application (RFAs) as a part of the BRAIN Initiative Program that encourage investigators to focus on noninvasive neuromodulation devices and techniques. Noninvasive devices "do not require surgery and do not penetrate the brain parenchyma" (BRAIN Initiative: Dose/Response, 2015). Innovative applications of noninvasive neuromodulation devices have the potential to elucidate alternative treatments to neurologic and psychiatric disorders, which may provide additional therapeutic options that do not carry the same risks as invasive therapies. In particular, the following two programs aim to go beyond incremental advances in order to thoroughly explore the relationship between noninvasive neuromodulation and the affected neural circuitry.

BRAIN Initiative: Noninvasive Neuromodulation—Mechanisms and Dose–Response Relationships for Targeted Central Nervous System Effects

The rapid advancement of scientific discovery has afforded the development of noninvasive neuromodulation devices as viable therapeutic options for the treatment of

some neurologic disorders. However, the understanding of the MOA of these devices has not advanced as swiftly. The objectives of this RFA (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-245.html) are to develop a fuller understanding of noninvasive neuromodulation device MOAs and to optimize new and existing technology through dose–response relationships in affected brain circuitry. Some suggested noninvasive devices include focused ultrasound, magnetic therapy, transcranial current stimulation, and transcranial magnetic stimulation (BRAIN Initiative: Dose/Response, 2015).

This RFA also seeks to develop a "systematic understanding" of stimulation paradigms and their effects on targeted locations or circuitry (BRAIN Initiative: Dose/Response, 2015). The expectation is that investigators will study the temporal, spatial, and contextual aspects during both resting and task-specific states and will elucidate the ramifications of these neuromodulatory aspects on both acute and chronic central nervous system (CNS) function. Additionally, this RFA asks investigators to consider the relationship between specific stimulation parameters and task-specific neural changes in varying circuitry, stimulation duration changes in network activity, and changes in the effectiveness of specific paradigms in circuitry of varying maturation. The focus of this RFA is to have a systematic understanding of both the MOAs of external noninvasive stimuli and spatiotemporal dose–response relationships for specific neural targets and processes, which is vital to the implementation of newly developed or optimized noninvasive neuromodulatory therapies for the treatment of neurologic disorders.

Brain Initiative: Noninvasive Neuromodulation—New Tools and Techniques for Spatiotemporal Precision

While the previous RFA focuses on an understanding of MOAs of noninvasive therapies, this RFA (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-240.html) creates a platform for the development of novel devices and techniques for noninvasive neuromodulation that are not reliant on or limited by the current standards of incremental advances in magnetic and electrical stimulation technologies. In fact, this RFA uniquely encourages non–hypothesis-driven development of devices that use novel transduction mechanisms.

This RFA is unique in other ways as well. Most important is its recognition of the fact that exploring novel therapies may include added risk to participant/subject or risk of the project failing to achieve successful outcome, but significant translational value may justify any additional liabilities. Because state-of-the-art magnetic and electrical stimulation paradigms lack spatial and temporal resolution, there is also opportunity under this RFA to encourage the collaboration of experts across scientific disciplines, including neuroscience, physics, engineering, psychiatry and psychology, and clinical practice. The partnership between various fields of study opens a dialogue centered on the exchange of specific knowledge that may not otherwise be readily accessible to individual investigators. This shift toward more collaborative research represents the dramatic possibility for the development of substantially more versatile, improved devices and techniques with real scientific and clinical benefit.

Improvements to the stimulation signal and dose are the main objective for devices and techniques proposed under this RFA. Available noninvasive neuromodulation techniques target large spatial regions of neural tissue, and methods to increase the focality, temporal control, and the creation of common standards for sham and control conditions are sought, as well as methods to eliminate off-target stimulation of nearby tissue. Additionally, in line with the priorities of the BRAIN Initiative as a whole, this RFA creates further opportunity for the optimization of chronic and closed-loop stimulation paradigms that will allow for the development of "devices that could be used outside the clinic" (BRAIN Initiative: New Tools, 2015) and would require less frequent clinical visits. Under this RFA, significant improvements to long-term stimulation and personalized medicine are possible with the potential to revolutionize current noninvasive neuromodulation program standards.

INVASIVE NEUROMODULATION STRATEGIES

Next-Generation Invasive Devices for Recording and Modulation in the Human CNS

The goal of this program is to support a streamlined path to advance promising novel stimulating and recording technologies by funding the FDA-mandated preclinical testing necessary to receive an Investigational Device Exemption (IDE) for Early Feasibility Clinical studies. A prerequisite for this RFA (https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-17-005.html) is that the proof-of-principle device must have been previously demonstrated in an appropriate animal model, are ready for accelerated manufacturing development under Design and Quality Systems Controls to conduct the benchtop testing, biocompatibility studies, and large-animal safety studies under Good Laboratory Practice.

As noted in the BRAIN 2025 report, "a single new stimulating or recording device for human up through FDA approval might cost $100 million or $200 million" (BRAIN, 2025, 2014). Consequently, the NIH is unlikely to support the cost of developing such a device all the way through the Feasibility and Pivotal Clinical Studies, necessary for FDA Pre-Market Approval (PMA) or

Humanitarian Device Exemption (HDE). These endeavors will have to be funded by venture capital and industry. However, there are key gaps in information and demonstrations that are necessary to reduce the risk of adoption, limiting the chances of follow-on venture capital or industry investment. This is addresed by facilitating Early Feasibility Studies aimed at responding to important scientific questions about the function of the device in human patients. This information is necessary to bridge the "valley of death" and to inform a final device design suitable for eventual FDA PMA and generate a complete business case and market path for sustainable commercial manufacture.

In traditional NIH study sections, these applications often have difficulties in review because a proof-of-principle had already been demonstrated in animal models, but a final device design with a description of the full-market path (including regulatory approval, insurance reimbursement, and sustainable commercial manufacture) was premature. The extensive and time-consuming preclinical testing necessary to receive an IDE to conduct pilot human studies was often perceived as less innovative. Moreover, preclinical testing to obtain FDA approval has a high attrition rate because the rigorous testing often unearths problems in device safety or design, which can either stop a project completely or require significant redesign and additional testing to solve. This serial dependency of inherently risky steps also creates issues in traditional review.

Finally, there are always lingering unknowns about the safety of the device or the extent and robustness of the intended therapeutic effect when making the leap from animal models to a more heterogeneous human population. Staged small trials demonstrating sufficient safety to expand into a trial in a larger population are effectively the only known method to protect vulnerable populations, grow scientific knowledge, and refine products for market approval. This latter point can create difficulties in NIH review for early feasibility clinical studies, as standard NIH review emphasizes appropriately powered and scientifically rigorous experimental design that requires a large number of patients to evaluate a therapy. Given that the first attempts in humans are intrinsically large leaps with several unknowns—and the focus of these initial steps is a staged and measured evaluation of safety—these review expectations can be problematic.

To address these difficulties, this program supports the submission of an IDE and execution of the subsequent pilot clinical study. Devices developed are not expected to meet the costly manufacturing standards necessary for a robust and reliable device. Instead, devices are only required to be manufactured to regulatory standards for safety in a highly controlled, short-term, chronic environment (1–2 years). Quantitative, specific milestones are developed and enforced by NIH program staff, and frequent interactions with the FDA are mandated. It is expected that the clinical study will inform a final device design that would have to go through most, if not all, of the preclinical testing on the path to more advanced clinical trials and market approval. This program also supports development of a device to test scientific hypotheses that are not feasible or practical to conduct in animal models but are critical for enabling next-generation devices.

THE BRAIN INITIATIVE PUBLIC–PRIVATE PARTNERSHIP PROGRAM

Approval for clinical studies can be very costly; therefore, it is economical to leverage existing devices in humans in order to prevent accruing the enormous expenses associated with preclinical testing of new devices. Even though market-approved devices may have wider research and therapeutic capabilities, they are labeled only for specific uses. In order to use these existing devices for experimental uses, investigators must work with the manufacturer to obtain additional regulatory approvals.

To expedite this process, the NIH BRAIN Public–Private Partnership Program (BRAIN PPPP) aims to "facilitate partnerships between clinical investigators and manufacturers of latest-generation stimulating and recording devices that are FDA-designated as Class III (defined as posing significant risk of harm) to conduct clinical research in the central nervous system" (BRAIN Initiative: Pre-applications, 2015). The RFA (see: https://grants.nih.gov/grants/guide/pa-files/PAR-15-345.html) introduces a much-needed framework that eliminates the traditional obstacles preventing industry and clinical experts from collaborating efficiently.

The central feature of the BRAIN PPPP is a set of template research agreements for collaborations between researchers, research institutions, and device manufacturers. These template agreements were generated with substantial input from industry partners, clinical researchers, the FDA, and representatives from institutional tech-transfer and contracts offices. They were refined from input at a workshop held on June 3–4, 2015 (video of the workshop is publically archived at http://braininitiative.nih.gov/meetings/June-2015-PPP.htm) along with public feedback from a request for information issued in the NIH guide (https://grants.nih.gov/grants/guide/notice-files/NOT-NS-15-032.html). Through these templates, the NIH aims to lower the barriers to using latest-generation devices for early stage clinical research and to broaden the knowledge base regarding the MOAs and potential therapeutic possibilities of those devices. Currently participating partners can be found at https://www.braininitiative.nih.gov/resources/BRAIN_PPP/PPP_devices_and_support.htm.

BIG DATA AND ETHICS OF NEUROMODULATION

Under the BRAIN 2025 Report, deliverables of "identifying fundamental principles" include new analysis techniques to accommodate complicated data sets produced by the BRAIN Initiative, novel integration methods for combining data resulting from various experimental designs, and improving data accessibility (BRAIN, 2025, 2014). The success of the BRAIN Initiative will be measured not only by the scientific, clinical, and technological advances in which it results but also by the ease with which collaboration is consequently facilitated between experts from various backgrounds in clinical, scientific, computational, and industry fields. The accessibility of data gathered under the BRAIN Initiative and the development of methods to standardize its analysis and comparison are crucial to the priorities of the program as a whole. As a result, the following RFAs aim to develop a foundation for the organization and maintenance of BRAIN Initiative data.

BRAIN Initiative: Data Archives for the BRAIN Initiative

The main objective of this RFA (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-255.html) is to "create the data infrastructures that will house the data from multiple experimental groups" (BRAIN Initiative: Data Archives, 2016). Given the enormous amount of data, both raw and processed, generated by work funded under the BRAIN Initiative, this RFA aims to support the development of multiple data archives that will allow for the management of these data. In a related RFA, "Standards to Define Experiments Related to the BRAIN Initiative" (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-256.html), the creation of data quality standards will allow investigators to upload relevant data and validate its quality, thus encouraging scientific rigor and reproducibility (BRAIN Initiative: Standards, 2016; Collins and Tabak, 2014; Landis et al., 2012). In particular, both invasive and noninvasive neuromodulation devices and techniques are listed as subdomains of data sets that may be in an available position for the development of data archives based on the quality standards indicated. An accessible database of validated and controlled neuromodulation data could significantly accelerate the translational pathway of novel neuromodulation therapies to clinical applications. It would enable direct access to relevant data on which to build the necessary corpus of material to support meta-studies and enable innovative experimental design through greater understanding of previous successes and failures.

BRAIN Initiative: Integration and Analysis of BRAIN Initiative Data

In addition to the creation of data archives, another crucial component of the BRAIN Initiative is the development of integrative visual and analytic software that will leverage the data archives and quality standards established under the previous RFAs. Software capabilities of particular mention in this RFA (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-257.html) include modifications to existing software or development of new software that enables parameter fitting and extraction, examination of dynamic space, unbiased cluster analysis, and future trend prediction and visualization and facilitates queries across multiple data repositories (BRAIN Initiative: Integration, 2016). Again, both invasive and noninvasive neuromodulation devices are noted as subdomains of the BRAIN Initiative that may already make use of software or related technologies that can be leveraged, modified, and improved under this RFA. Software refined under this mechanism would have critical implications for the use and distribution of BRAIN-related data because it would enable the synthesis of multiple datasets. This cross-data collaboration could even reveal otherwise overlooked links between small- and large-scale research, contributing substantially to the BRAIN Initiative priority of a whole brain connectome.

Research on the Ethical Implications of Advancements in Neurotechnology and Brain Science

As with any rapidly developing scientific field, ethics quickly become a concern as novel approaches begin to show clinical therapeutic benefit. Under this RFA (see: https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-260.html), investigators are asked to consider current and future ethical concerns related to research developed under the BRAIN Initiative. While neuroscience may imply a host of ethical issues not relevant to other fields of study because the brain is the center of human consciousness, issues related to the treatment and protection of data are also highly important. Of particular interest under this RFA are ethical studies describing issues related to stimulation effects on personal identity or agency as well as to data ownership, privacy, intended and unintended use, infrastructure maintenance and security, and matters related to informed consent (BRAIN Initiative: Ethical Implications, 2016). Both invasive and noninvasive neuromodulation therapies require informed consent of participating patients, which would include

the obvious physical risks associated with such procedures. However, this RFA asks investigators to consider the circumstances under which data collection and distribution relevant to the priorities of the BRAIN Initiative may pose any ethical dilemmas. Data ownership, patient privacy protection, and even the implications of ethical accessibility to data are swiftly growing in importance as emerging technological advancements in neuromodulation allow for greater and greater access to the human brain.

DARPA PROGRAMS FOR NEUROSCIENCE AND NEUROTECHNOLOGY

DARPA is a funding agency tasked with developing breakthrough technologies for the U.S. Department of Defense. DARPA does not fund broad-based research programs but instead seeks to make pivotal investments in nascent areas of science and technology with the goal of identifying new opportunities or threats that may impact U.S. national security. To lead these efforts, DARPA actively recruits scientists and engineers in targeted fields of interest to serve as program managers (PMs). These positions are term-limited, rarely exceeding four years, and the continuous turnover ensures a steady influx of fresh ideas.

When deciding which new programs to support, every DARPA PM must answer the Heilmeier Catechism, created by George H. Heilmeier, DARPA director from 1975 to 1977, which includes:

1. What are you trying to do? Articulate your objectives using absolutely no jargon.
2. How is it done today, and what are the limits of current practice?
3. What is new in your approach, and why do you think it will be successful?
4. Who cares? If you succeed, what difference will it make?
5. What are the risks?
6. How much will it cost?
7. How long will it take?
8. What are the mid-term and final "exams" to check for success? (The Heilmeier Catechism, 1975)

These criteria of the Heilmeier Catechism have been compared with other technology investment criteria but are generally meant to understand how a strategic investment by DARPA could provide a needed solution, disrupt a sector, or even create a new one. DARPA PMs work with the research community to assess the current limits of practice and put forth a grand challenge, which is subjected to the Heilmeier Catechism and defended by the PM to the leadership of the agency. These grand challenges are formulated as broad agency announcements to solicit solutions from the research community. Often, these challenges seek to enable a new breakthrough at a rapid pace and require an intense, collaborative effort among experts drawn from a wide range of specialties. Uniquely for a funding agency, DARPA programs are not designed to support the growth of a discipline. There is usually only one receipt date for proposals, investigators are selected at the beginning of the program, and each project has a pre-determined end date.

The Heilmeier Catechism is also applied to all proposals under consideration for funding, pervading the program's design with a focus on the risks, costs, and timeline. Because the research is high risk/high reward, there is an expectation that not every effort will achieve all of the projected goals; therefore, periodic evaluations and go/no-go criteria are built into the award to enable decisions about continued funding or shifts in direction. In this system, the PM has significant freedom to shape the course of the program and ultimately redefine the state-of-the-art.

Because DARPA is tasked with advancing the leading edge of technology, DARPA programs are often the first to reveal new societal dilemmas that emerge from the novel capabilities being developed. In doing so, DARPA's leadership and PMs understand that these pursuits may sometimes raise ethical, legal, security, or policy questions that cannot and should not go unaddressed. To consider these issues, DARPA engages experts in ethical, legal, and societal implications early on in its program development process.

DARPA also has a long history of supporting research in neuroscience and neurotechnology, starting in the 1970s with a brain–machine interface (BMI) program titled Close-Coupled Man/Machine Systems (later renamed Biocybernetics). The Biocybernetics program focused on many themes that remain central to modern research in BMI, such as using electroencephalography to communicate commands or monitor neural states associated with vigilance, fatigue, emotions, decision-making, perception, and general cognitive ability (Miranda et al., 2015). DARPA continues to explore opportunities for neurotechnology, given the need to treat neurologic and physical disabilities sustained by service members.

The following programs are a few recent examples of investments DARPA has made to enable new technologies to study and interface with the brain in support of the BRAIN Initiative.

Revolutionizing Prosthetics Program Phase 3

The Revolutionizing Prosthetics Program was launched in 2006 with the goal of creating robotic arms that match the form and function of a human arm and

hand, including natural control and sensory functions. While the early phases of the program focused mainly on designing and creating anthropomorphic robot arms, the final phase of the program was focused on establishing a direct brain interface for control and sensation (Flesher et al., 2016).

Reliable Neural-Interface Technology

The Reliable Neural-Interface Technology (RE-NET) program, launched in 2010, addressed the unsolved problem of neural interface longevity when implanted in animals and humans. The use-case driving this need was control of dexterous prosthetic limbs. This program focused on developing the necessary technologies to reliably record from the nervous system for decades and to demonstrate that the neural information could control a prosthesis. The RE-NET program aimed to fundamentally understand the biological and electrochemical issues that affect neural interfaces durability through study of histology for interface stability over time, and to develop solutions for reliable central and peripheral nervous system interfaces.

Restoring Active Memory

DARPAS's Restoring Active Memory (RAM) program goal is to develop and test a "closed-loop" wireless, fully implantable, neural-interface medical device for human clinical use to facilitate memory recall. RAM includes concomitant development of multi-scale computational models with high spatial and temporal resolution in order to comprehensively understand memory.

Systems-Based Neurotechnology for Emerging Therapies

The Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program goal is to create full neuromodulation therapy as an implanted "closed-loop" diagnostic and therapeutic system for treating a variety of neuropsychological illnesses. This program is developing a fundamental understanding of the circuit dysfunction that occurs in neuropsychiatric disorders with the goal of diagnosing and correcting the circuit level dysfunction.

Neuro Function, Activity, Structure, and Technology

The Neuro Function, Activity, Structure, and Technology (Neuro-FAST) program aims to enable generation of technologies that have improved spatial and temporal precision. The goal is to visualize and characterize activity in the brain and then decode this information to better mitigate threats and improve behavioral outcomes. Several groundbreaking technologies have been de-risked and disseminated in this program, including the CLARITY technique. CLARITY is a method to characterize the anatomical and functional connectivity of various neuromodulation therapies in an *ex vivo* preparation by rendering opaque tissue transparent (Chung et al., 2013).

Neural Engineering System Design

The goals of Neural Engineering System Design (NESD) are to develop a clinically viable, implantable neural interface that is capable of providing an orders-of-magnitude improvement in the specificity and scale of communication between brain tissue and a neural interface and to develop the algorithms to translate this information between the digital and neural domains. This program seeks to develop, validate, and demonstrate manufacturing processes for a biocompatible device that is no larger than one cubic centimeter.

Targeted Neuroplasticity Training

The Targeted Neuroplasticity Training (TNT) program was announced in 2016, with the goal of developing neuromodulation technology that accelerates learning processes by enhancing synaptic plasticity in the brain during training. Prior research has shown that stimulation of peripheral nerves such as the vagus nerve (Engineer et al., 2011) can enhance auditory cortex map plasticity in the rat, and even enhance therapies for tinnitus in humans (De Ridder et al., 2013). The TNT program is aimed at understanding the function of neural circuits engaged by neurostimulation of peripheral nerves thought to play a role in regulating attention, arousal, and plasticity. This knowledge will be used to design neuromodulation technology to boost synaptic plasticity in the brain, thus enhancing learning processes during training.

Reorganization and Plasticity to Accelerate Injury Recovery

The Reorganization and Plasticity to Accelerate Injury Recovery (REPAIR) program focused on research regarding neural reorganization mechanisms through the combination of local and network brain imaging. REPAIR relied on the development of new approaches to multiscale recording in order to develop a model of neural signaling from initial cues through task completion to enhance understanding of rehabilitation following brain injury.

Restorative Encoding Memory Integration Neural Device

The Restorative Encoding Memory Integration Neural Device (REMIND) program was launched to develop a brain implant that will restore memory and cognitive function that has been lost as a result of injury. Initially, the program was intended for soldiers who have been injured in combat, but it could have implications for the treatment of other cognitive and memory disorders.

FDA SUPPORT OF BRAIN NEUROMODULATION THERAPY PROGRAMS

The FDA Center for Devices and Radiological Health (CDRH) has played a critical role in the formation of the NIH BRAIN and DARPA BRAIN Programs. As part of both the NIH and DARPA efforts, the FDA Division of Neurological and Physical Medicine Devices provided feedback on the goals of each translational program as well as during the application review process. Perhaps more importantly, in 2011, the FDA announced an Early Feasibility Study program, which aimed to ease the road to market approval through "limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication" (Early Feasibility Study, 2013). This program allows investigators to establish proof-of-principle and safety and reliability data for clinical devices still under development. It effectively accelerates the pathway to market approval because it expedites the numerous, often expensive, safety testing required for first-in-human studies. The FDA's support of BRAIN neuromodulation therapy programs is invaluable because of the need for partnership between government and industry in order to commercialize a safe device.

NATIONAL SCIENCE FOUNDATION NEUROMODULATION INITIATIVES

The NSF also plays a fundamental role in the BRAIN Initiative by facilitating the generation of an array of tools that are necessary to determine the building blocks and emergent properties of healthy brain function and the effects of neuromodulation therapies on these functions (BRAIN: Brain Research, 2016). Additionally, the NSF has invested in creating and maintaining a strategic workforce to invent, develop, and implement the necessary infrastructure and next-generation neurotechnology that will provide a more comprehensive understanding of the dynamic properties of the brain. The NSF has set out to address these issues by defining five thematic areas for involvement, which will have a great degree of impact on neuromodulation therapies and understanding the underlying MOAs. These thematic areas include:

1. **Multiscale integration of the dynamic activity and structure of the brain** to elucidate and link local and global brain function with meaningful behavioral outcomes, including measuring the real-time physiologic, behavioral, and cognitive outputs,
2. **Neurotechnology and research infrastructure** designed to create the necessary tools to measure changes in the brain and correlate them with complex behaviors, while also implementing data sharing systems that enable crosstalk and accelerate advancement of the field,
3. **Quantitative theory and modeling of brain function** to develop models designed to capture the emergent properties of the brain to inform future predictive theoretical framework,
4. **Brain-inspired concepts and designs** to strategically build on the lessons learned in the BRAIN Initiative to inform future generation technology, and
5. **BRAIN workforce development** to advance the field by disseminating knowledge across a BRAIN workforce while also creating new career opportunities for BRAIN discovery and innovation.

BEYOND "THE BRAIN": RELATED PROGRAMS

DARPA Programs

Hand Proprioception and Touch Interfaces

The Hand Proprioception and Touch Interfaces (HAPTIX) program is aimed at bringing together several advanced technologies to enable natural control and sensation of a prosthetic limb. Understanding the neuroscience of touch and proprioception are the foundation to restoring sensation in amputees, and the end-goal of this program is to develop new metrics to quantify sensation and the benefits gained by amputees from restoration of their sensation. In order to achieve this, the program has funded teams to develop a take-home trial of a sensorized prosthetic hand and wireless implanted neural interface system for human volunteers. The technologies will not only be able to record and stimulate biological tissues to restore function but also serve as platforms that can be employed in many other research and clinical settings for other diseases.

Electrical Prescriptions

The Electrical Prescriptions (ElectRx) program aims to create technology for improving physical and mental health by using targeted stimulation of the peripheral nervous system. The goal is to create devices that can access the sophisticated networks of peripheral nerves that continuously monitor and regulate functions of visceral organs and the brain. Technology development focuses on novel neural interfaces using optical, acoustic, electromagnetic, or engineered biology strategies to achieve precise targeting of peripheral nerve fibers for long-term monitoring and modulation. Technology development efforts in ElectRx are grounded firmly in studies of the anatomy and physiology of specific neural circuits and their role in health and disease. Coupling improved physiologic understanding with improved neural interface technologies could lay the foundation for future systems to manage many acute and chronic conditions through precise, real-time, closed-loop neuromodulation. If successful, this capability would reduce dependence on traditional drugs and create new treatments that could be tuned automatically and continuously to the needs of individuals without side effects.

NIH Programs

Stimulating Peripheral Activity to Relieve Conditions

Complementary to the ElectRx program, Stimulating Peripheral Activity to Relieve Conditions (SPARC) is developing the scientific foundation for the next generation of therapeutic closed-loop neuromodulation devices. SPARC investigators will construct an open atlas of comprehensive anatomy and functional peripheral nerve connectivity with organs. In conjunction with development of the atlas, the scientific gaps to be addressed include understanding the specific and diverse peripheral neural signals carried by nerve fibers to or from end-organs; understanding the functional relationships between neural signals and end-organ cellular activity; developing tools, techniques, and mechanisms to functionally modulate specific portions of peripheral nerves; and validating particular animal models to human neuroanatomy and functional neurobiology of organs. In collaboration with industry partners, SPARC investigators will produce proofs of concept for new nerve stimulation indications and will study functional neuromodulation in the context of human clinical studies.

Projects in such an immature field will require facilitated coordination among experts in anatomical, physiological, and functional mapping, biologists specializing in each organ system, surgeons who routinely access nerves for each organ system, technologists with expertise in multiple technologies, and translational engineers. In parallel, important technologies for generating the high-resolution functional maps and for enhanced therapeutic targeting will be developed along different and unpredictable timelines. Consequently, the SPARC Program is using a non-grant vehicle called "other transaction awards," similar to how DARPA funds research, to implement a novel management strategy tailored to create a highly responsive and fluid program, yet with the goal of producing a corpus of knowledge.

National Institute of Neurological Disorders and Stroke (NINDS) has also provided notice of their intent to publish a new funding announcement to support development of translational neural devices. This is distinct from the BRAIN Initiative, in that supported projects would not be limited to disorders of the central nervous system. In addition, the program will be focused on developing therapeutic and diagnostic technologies, instead of developing tools to study the nervous system. The program is structured to support milestone-driven projects with firm go/no-go decision-making. The projects will have an initial phase to support translational device activities leading to submission of an IDE to the U.S. Food and Drug Administration (FDA) or Institutional Review Board (IRB) application for a nonsignificant risk (NSR) study. Only projects receiving regulatory approval and meeting all milestones will be eligible for transition to the second phase, supporting an Early Feasibility Study or a small clinical study. The initiative is planned as a successor to the prior NINDS Cooperative Research to Enable and Advance Translational Enterprises (CREATE Devices) program that ended in early 2017. It is expected that devices within the scope of this program are very close to the "final system" and would be manufactured using a manufacturing process nearly identical to the ultimate device to be marketed or studied in a larger clinical trial.

CONCLUSION

The BRAIN Initiative is not unlike the HGP. Completely sequencing the human genome has not led to a finite conclusion but instead has led to an increasingly dynamic picture of the functional genome. However, it is still inexorably dependent on a fundamentally static genome. Similarly, the human nervous system appears to have functional components that are highly similar or even completely unchanging from individual to individual, as well as components that are specific to the individual, yet relatively static. There are also physiologic principles that are consistent across

individuals which govern dynamic changes in neural function.

Just like the movement toward personalized pharmacologic and biological medicines, the future of neuromodulation therapies is dependent on the development of new tools to identify both the static and dynamic portions of functional maps of the central and peripheral nervous systems across individuals and foundational understanding of the mechanisms underlying neuromodulation and circuit functionality. Only through the understanding of these static and dynamic components of the functional map of the human nervous system at both the individual and population levels can we directly observe the overall physiologic consequences of neuromodulation therapies and thereby optimize these therapies to achieve the best outcomes across the largest number of patients.

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